Operating review of 2004

This is our review of Acambis' performance during 2004, which was a year of mixed fortunes with developments in all the key areas of our business: our smallpox franchise; our travel vaccine sales; and our R&D pipeline.

The ups...	The downs...
ACAM2000 155 million-dose and 27.5 million-dose US Government orders completed	Expected US Government order for 26.5 million doses of ACAM2000 not placed
Reduced cost from early close-out of ACAM2000 Phase III trials increased gross margin	Clinical hold on ACAM2000 Phase III trials from April to September
ACAM2000 sales to three other governments	ARILVAX BLA withdrawn
ChimeriVax-West Nile: first-ever human clinical trial results	ChimeriVax-West Nile delay from analysis of adverse events, believed to be related to strenuous exercise
Fast-track status award to ACAM2000 and MVA	
Won second US Government MVA contract	
First sale of C-VIG	
New management team established	

SMALLPOX FRANCHISE UPDATE

ACAM2000

Preparations for the possibility of a smallpox outbreak continue to have a high profile internationally. In November 2004, the WHO published a report on smallpox that is to be put before the World Health Assembly in May 2005. In it, the WHO highlighted that 'timely administration of vaccine according to well-established epidemiological principles has historically been effective in rapidly containing smallpox outbreaks. Vaccine stocks currently held by countries are, however, unevenly distributed and of uncertain quality'.[1] The report outlined plans for a five million-dose vaccine stockpile to be held by the WHO in Geneva and for a 'virtual' stockpile of up to 200 million doses that countries pledge to make available to the WHO in the event of an outbreak. It also supports the concept of maintaining 'standby capacity', i.e., warm-base manufacturing, in at least two countries around the world.

The US Government continues to take the lead in preparations. Although we were disappointed that the US CDC did not place an additional order of 26.5 million doses of ACAM2000, we are confident that the US Government remains committed to smallpox preparedness.

We have submitted a proposal to the CDC for Acambis to provide the US Government with an ongoing warm-base manufacturing capability. It proposes that this activity commence in 2005 and continue for several years thereafter. We await a final decision on our proposal from the CDC.

Since the lifting of the clinical hold on ACAM2000 in September, which had been placed on the Phase III trials in April 2004 by the FDA following identification of a small number of cases of the heart-related condition myocarditis, we have been closing out the trials and analysing the safety and efficacy data. We are planning to file the BLA with the FDA in the second half of 2005 and hope to have a decision on our application during 2006. Cost savings

associated with closing the trials early had a positive effect on the gross margin for this fixed-price contract.

We believe that if ACAM2000 is approved by the FDA, licensure could be instrumental in achieving further sales to other governments. In 2004, our share of sales to other governments generated £6m in revenue to Acambis and we are confident that, based on an assessment of discussions currently ongoing, we will be able to achieve at least a similar level of sales in 2005. Since the beginning of 2005, we have already completed one further government contract.

C-VIG

During 2004, we received our first government order for Cangene's investigational C-VIG and are in discussions with a number of other governments. As a treatment for adverse reactions to smallpox vaccination, VIG is recommended for any government stockpiling smallpox vaccines. We act as Cangene's agent outside North America and Israel. Cangene has submitted a BLA to the US FDA to seek licensure of C-VIG.

MVA

We are currently evaluating MVA, an attenuated smallpox vaccine, in human clinical trials under a US IND application. The clinical trials are being conducted to assess whether MVA is safe and effective for use by the proportion of the population for whom standard smallpox vaccines are contraindicated. In the US, this represents an estimated 10% to 20% of the population.

In September, we were one of two companies to win a second US Government contract for the development and manufacture of investigational MVA vaccine from the NIAID, part of the US NIH. We are co-developing our MVA vaccine candidate with Baxter. Our contract is potentially worth up to $131m.

Under the principal part of this contract, worth approximately $76m, we are conducting a series of clinical trials and demonstrating our ability to scale up our production processes by delivering 500,000 doses of vaccine. The second part of the contract, which is an option awardable at the discretion of the NIAID, would be worth approximately $55m and require delivery of a further 2.5 million doses of MVA. Work is progressing well under the principal part of the contract and, with the clinical testing programme, will continue through 2007, with the majority of the work being conducted during 2005 and 2006.

Successful performance under this contract is critical to establishing a strong competitive position when bidding for the larger stockpiling contract the US Government has indicated it intends to issue under Project Bioshield, which was signed into law in July 2004. The US Government has not yet indicated when it will issue a Request for Proposals inviting tenders for the MVA stockpiling contract or its timeline for contract award. We are monitoring the situation closely and remain confident that, together with our partner Baxter, we are in a strong competitive position in bidding for the contract.

TRAVEL VACCINE FRANCHISE UPDATE

In its first full year as an Acambis subsidiary, BPC performed extremely well, with its sales of the oral typhoid vaccine, Vivotif, well ahead of the previous year's. Furthermore, sales in the first two months of 2005 were ahead of the equivalent period in 2004.

CLINICAL DEVELOPMENT UPDATE

ARILVAX

We have US marketing rights to this yellow fever vaccine from its owner and manufacturer, Chiron Vaccines. Having completed all clinical trials required to apply for licensure of ARILVAX in the US, we submitted a BLA to the FDA in December 2003. However, we withdrew the application in February 2004 because Chiron Vaccines had indicated the requisite Pre-Approval Inspection by the FDA of its manufacturing facility would not be possible within the 10-month BLA review timeframe. Following a project review, we will not now be in a position to resubmit the BLA within the previously indicated timescale of the first half of 2005. At this stage, it is premature to indicate when the resubmission will take place. The revised timelines and regulatory strategy are the subject of discussion between the companies.

CHIMERIVAX-JE

JE is a mosquito-borne viral disease that affects much of Asia and parts of Australia. According to the WHO, 50,000 human cases of JE are reported annually in Asia, resulting in 15,000 deaths, although the true incidence is probably higher as surveillance and reporting rates are poor.[2]

ChimeriVax-JE is the most advanced of the vaccines we are developing based on our proprietary ChimeriVax™ technology. JE vaccines have been available for many years but there is a recognised need for development of a second-generation JE vaccine that is safer, requires fewer doses and can be used more readily in developing countries.[3] The major markets for ChimeriVax-JE would be endemic populations and travellers/military personnel from overseas who are visiting endemic regions.

1 WHO EB115/36 (23 December 2004)
2 WHO Initiative for Vaccine Research (www.who.int)
3 Ibid. (www.who.int)

'With the ups and downs of 2004 now behind us, we are looking forward to 2005 as a year of investment, aimed at driving our product pipeline forward and expanding our product portfolio.'

GORDON CAMERON

The 'bridging' trial that we are conducting is now fully recruited. This follows our strategic decision in 2003 to bring commercial-scale manufacture of ChimeriVax-JE in-house and to finalise scale-up of our manufacturing process to optimise a stable, freeze-dried formulation prior to undertaking Phase III clinical testing. The bridging trial aims to confirm that the new material has a clinical profile similar to that seen in previous trials of the vaccine. Once complete, we plan to initiate Phase III trials in the second half of 2005.

CHIMERIVAX-WEST NILE

West Nile, which is a mosquito-borne virus closely related to JE, is causing particular problems in the US where it was first identified in 1999. Since then, there have been more than 16,000 cases and 650 deaths related to West Nile virus.[1]

In May 2004, we became the first company to publish results from a human clinical trial of a West Nile vaccine with data from the first cohort of a Phase I trial. Of the 15 subjects vaccinated with ChimeriVax-West Nile in the first cohort, 100% developed West Nile-neutralising antibodies within 21 days of receiving a single inoculation. These data were published following the unblinding of data from the first cohort vaccinated in our Phase I trial. Two adverse events were noted, which we believe were caused by strenuous exercise. A paper on this subject was recently published in *Human Vaccines* (1:1, Jan-Feb 2005). The protocol was consequently amended to include a placebo group instead of a yellow fever comparator. Two further cohorts, making a total of 80 subjects, have now been recruited and vaccinated in the trial. We elected not to recruit subjects for the final, lowest-dose cohort as we felt the data would not have been useful to product development objectives and timelines. Data analysis is ongoing and we expect to publish preliminary results from the completed trial in the first half of 2005 and to initiate the next phase of trials in the second half of the year, using material we have manufactured ourselves.

CHIMERIVAX-DENGUE

Dengue is a mosquito-borne viral infection that, in recent years, has become a major health concern. The WHO estimates that there are approximately 50 million dengue infections each year and that more than 500,000 cases of the more severe form of the disease, dengue haemorrhagic fever, require hospitalisation each year.[2] As there are four distinct dengue virus serotypes, a successful vaccine will need to protect against all four.

Rights to Acambis' tetravalent (four-component) ChimeriVax-Dengue vaccine are licensed to SP, which fully funds the development programme. We are entitled to milestone payments and a royalty on any sales. Preliminary safety data are available from a Phase I trial of our tetravalent vaccine. SP is expected to publish the data when comprehensive validated Phase I safety and immunogenicity data are available. As planned in the licence agreement between Acambis and SP, responsibility for manufacturing and for further clinical testing is with SP. SP is proceeding to the next phase of clinical trials and is engaged in industrial scale-up of the product. Acambis will continue to be involved in the programme through to licensure of the product as part of a joint steering committee.

C. DIFFICILE

Clostridium difficile bacteria are often found in institutional settings such as hospitals and nursing homes. Treatment with antibiotics can permit these bacteria to over-populate the colon and cause *C. difficile*-associated diarrhoea (CDAD) by releasing two toxins. CDAD can be recurrent and life-threatening.

The vaccine we are developing aims to stop the recurrence of CDAD, which occurs in approximately one in five CDAD patients after standard treatment. However, the rising incidence and severity of this infection may also justify clinical development towards a primary prevention indication. We have previously conducted Phase I trials of our vaccine but discontinued these when we found that the vaccine lot in use was losing its potency four years after manufacture. We have recently completed the development of a new, more robust and scaleable in-house manufacturing process. We are now returning to clinical testing with two Phase I trials planned to commence in the first half of 2005.

BUSINESS DEVELOPMENT UPDATE

As part of our efforts to develop a more predictable revenue stream, we are pursuing opportunities to acquire, in-license or co-market products. We are particularly interested in revenue-generating products that can be sold through BPC, where these can be channelled through the existing infrastructure at marginal cost. We are also looking to leverage our clinical and regulatory expertise and manufacturing infrastructure to partner in projects with companies that are seeking to benefit from such capabilities or experience.

Our balance sheet strength, and particularly our cash and short-term investments balance of more than £100m, gives us considerable flexibility in pursuing such opportunities.

EMPLOYEES

We continue to monitor headcount closely to ensure it matches the current and future needs of the business. At 31 December 2004, our Group headcount was 270 (2003 – 320). The decrease seen in 2004 was a result of the closure of the UK Research department, announced in January 2004, following the decision to consolidate our Research operations in the US.

1 US CDC (www.cdc.gov)
2 WHO fact sheet No.117 (www.who.int)

Financial review of 2004

The financial results for the year ended 31 December 2004 are presented below.

TRADING RESULTS

Revenue for the year was £85.5m (2003 – £169.1m). As in 2003, the main sources of revenue were the fixed-price 155 million-dose ACAM2000 contract with the CDC and its order for an additional 27.5 million doses of the vaccine. The reduction compared with 2003 reflects the fact that the majority of the work under the 155 million-dose contract was undertaken in 2002 and 2003. During the year, we continued to record revenue from sales of ACAM2000 to other governments. We also recorded revenues from our two contracts with the NIAID in respect of our MVA programme, the second of which was awarded in September 2004, from sales of Vivotif and from SP for our ChimeriVax-Dengue vaccine programme.

Cost of sales in 2004 decreased to £34.3m (2003 – £98.4m), in line with revenues. These relate to all of the above revenue except costs on the ChimeriVax-Dengue programme, which are recorded within R&D costs.

Our gross profit margin for the year increased sharply to 59.9% (2003 – 41.8%). This represents the change in the mix of revenues recorded in the two years. It was also impacted by the reassessment of costs under the 155 million-dose contract following the decision to close out the two Phase III clinical trials early and expensing of certain costs to R&D costs as the manufacturing facility was used to support our proprietary vaccine development programmes.

Expenditure on R&D increased significantly in the year to £28.9m (2003 – £19.9m) as a result of the progression of our projects into later stages of development and the process development and manufacturing work for our R&D projects.

Sales and marketing costs, which include both Acambis' internal sales and marketing infrastructure and our BPC operation, which we acquired in August 2003, were £2.7m (2003 – £1.3m). The increase principally reflects a full year of costs in 2004 associated with BPC. Administrative costs, including amortisation of goodwill, increased to £5.1m (2003 – £4.5m) as a result of the acquisition of BPC.

During the year, the Group recorded two items related to the Canton manufacturing facility. Firstly, in May, we announced that we had reached a c. £10.6m ($19.0m) settlement with Baxter in respect of the termination of the Canton manufacturing agreement. £10.2m of that income has been recorded as exceptional other operating income during the year. The balance of £0.4m is recorded within interest receivable and similar income to reflect the staged-payment nature of the agreement, with £0.2m recorded during 2004 and the remaining £0.2m to be recorded during 2005. The first £5.1m ($9m) due under this agreement was received in 2004 and the second instalment of £2.6m ($5m) was received in January 2005. The third and final instalment of c. £2.6m ($5m) is payable in January 2006.

Secondly, as a result of this agreement with Baxter, we also recorded during the year a non-cash impairment charge of £1.9m ($3.5m) as an exceptional administrative item, which related to certain of the fixed assets in the plant for which, as a result of terminating our agreement with Baxter, we no longer had a use. The net income recorded by these two transactions was £8.3m (2003 – £nil).

The Group recorded a further exceptional administrative item of £0.7m (2003 – £nil) associated with the restructuring of the Research operations and the closure of the UK Research department, announced in January 2004.

Interest receivable increased significantly in 2004 to £4.6m (2003 – £2.1m) as a result of higher average levels of cash and interest rates throughout the period. In 2004, the Group sold its investment in Medivir AB for £0.7m, resulting in a loss of £0.1m in 2004. Interest payable reduced marginally in 2004 to £0.9m (2003 – £1.0m), representing primarily interest payable on the lease-financing facility that was put in place for the reactivation of our manufacturing plant. During 2004, an exchange gain of £0.3m (2003 – £0.4m) was recorded as a result of the revaluation of the amounts outstanding under our US dollar-denominated debt facility for our ARILVAX programme.

Pre-tax profit for 2004 was £26.2m (2003 – £39.6m). This reduction is in line with expectations, principally as a result of a lower level of activities on the ACAM2000 155 million-dose CDC contract.

In 2004, we recorded a tax charge of £6.4m (2003 – £3.9m). The effective tax rate for 2004 was 24.4% (2003 – 9.8%). This is lower than previously expected as a result of more effective utilisation of Group tax losses.

CAPITAL EXPENDITURE

Capital expenditure in 2004 was lower at £3.6m (2003 – £6.0m). Expenditure during the year related predominantly to the cost of redeveloping and expanding areas of our US R&D facility. We expect expenditure levels in 2005 to be similar to those seen in 2004.

BALANCE SHEET HIGHLIGHTS

I) CASH/DEBTORS

Cash and short-term investments of the Group at 31 December 2004 amounted to £101.8m (2003 – £125.2m). The reduction in cash during the year is a result of the working capital movement associated with our 155 million-dose CDC smallpox vaccine contract.

During the year, Debtors: amounts receivable within one year increased to £15.6m (2003 – £12.3m), principally as a result of the amount owed by Baxter for settlement of the Canton manufacturing agreement.

II) STOCK/CREDITORS: AMOUNTS FALLING DUE WITHIN ONE YEAR

Stock held at 31 December 2004 amounted to £6.0m (2003 – £18.2m). The reduction seen in the year is a result of having shipped ACAM2000 vaccine doses to our largest customer, the CDC, to complete the 155 million-dose order and fulfil the 27.5 million-dose order, and also to other governments. The balance principally represents work-in-progress and finished goods in relation to our ACAM2000 smallpox vaccine.

Our adopted method for recognising revenue under the ACAM2000 contract with the CDC, which involves the recognition of revenue in line with the degree of completion of the contract, continues to give rise to a significant difference between invoices submitted and amounts recognised as revenue. During the year, the amount recorded as deferred income under this contract reduced significantly to £16.5m (2003 – £49.5m) as a result of activities being completed on the contract. This is included within the total Creditors: amounts falling due within one year of £46.2m (2003 – £96.9m). This level of creditors will reduce further during 2005 as revenues under the 155 million-dose contract continue to be recognised.

III) LEASE FINANCING AND OVERDRAFT FACILITIES

We have two US dollar-denominated financing facilities. The balance on our Canton lease-financing facility at 31 December 2004 was £9.4m (2003 – £12.6m). The reduction represents capital repaid in the period in accordance with the terms of the facility. The balance on the ARILVAX overdraft facility at 31 December 2004 was £3.6m (2003 – £3.9m).

We are maximising our revenue-generating opportunities to enable us to progress and expand our pipeline of new, innovative vaccines.

DAVID LAWRENCE

	YEAR ENDED 31 DEC 2004	YEAR ENDED 31 DEC 2003
REVENUE	£85.5m	£169.1m
PRE-TAX PROFIT	£26.2m	£39.6m
EARNINGS PER SHARE	18.6p	34.7p
EARNINGS PER ADR*	$0.71	$1.24
CASH	£101.8m	£125.2m

*Based on ratio of one ADR to two ordinary shares

IFRS

IN CONJUNCTION WITH ERNST AND YOUNG LLP, WE HAVE CONDUCTED A PRELIMINARY REVIEW OF THE FINANCIAL IMPLICATIONS OF APPLYING IFRS, WHICH WILL BE ADOPTED BY THE COMPANY FOR ITS FINANCIAL RESULTS WITH EFFECT FROM 1 JANUARY 2005.

SARBANES-OXLEY

AS A FOREIGN REGISTRANT, ACAMBIS IS REQUIRED TO COMPLY WITH THE PROVISIONS IN SECTION 404: MANAGEMENT ASSESSMENT OF INTERNAL CONTROL (S404) OF THE SARBANES-OXLEY ACT 2002. THE AUDIT COMMITTEE AND THE BOARD REVIEW REGULARLY OUR PROGRESS ON ACHIEVING COMPLIANCE WITH S404 AND IN 2005 WE WILL TEST REGULARLY THE VARIOUS CONTROLS WE HAVE IDENTIFIED. FOR MORE INFORMATION, PLEASE REFER TO PAGE 14.

Financial systems

THE FOLLOWING SECTION SETS OUT SOME OF THE MAIN FINANCIAL PARAMETERS THROUGH WHICH WE MANAGE OUR BUSINESS.

TREASURY POLICY

The Group holds the majority of its cash in sterling but also holds some in US dollars and euros. Where considered surplus to working capital requirements, the Group converts US dollars and euros into sterling on an ongoing basis, which currently attracts a higher interest rate and mitigates certain exchange rate exposures, given our reporting currency is sterling.

We manage our cash in money market funds with the aid of professional money market managers. The Board reviews the performance of those funds to ensure they achieve competitive rates of return. Our treasury policy ensures that our capital is not at risk. During 2004, we hedged certain foreign exchange exposures. At 31 December 2004, the Group had a dollar forward contract outstanding which settled in January 2005. We manage this area on an ongoing basis to ensure that, where possible, potential areas of risk are appropriately mitigated.

Of the £13.0m ($25.0m) US dollar-denominated debt (as referred to within 'Current Liquidity' below), the interest rate payable on the $18.0m (£9.4m) finance lease is fixed at 6.25% per annum for the life of the lease; and the $7m (£3.6m) ARILVAX overdraft facility is charged at 0.35% per annum above the bank base rate for US dollars.

CURRENT LIQUIDITY

At the end of 2004, Acambis had just over £100m invested in cash and short-term investments. Our strong cash balance since 2003 has meant we have not had to increase our debt in the last couple of years.

At 31 December 2004, we had £13.0m ($25.0m) of US dollar-denominated debt on our balance sheet, comprising a lease-financing facility for the reactivation of our manufacturing plant and an overdraft facility for the ARILVAX programme. Under the current terms of these arrangements, both these debts will be repaid within the next two years. In 2001, £14.0m ($18.6m) of a potential c. £21m ($40m) was drawn down from the lease-financing facility. We do not envisage utilising the undrawn amount and started to repay the capital in 2004.

CASH FLOW

During 2004, the net cash and liquid resources outflow for the Group was £23.4m; of this, £19.5m was attributable to operating activities and £3.9m to investment, taxation and financing activities.

INTERNAL SOURCES OF LIQUIDITY

The Group has a number of inter-company agreements between its companies that have historically been put in place to secure the long-term funding requirements of each of those companies.

GOING CONCERN STATEMENT

The Directors have a reasonable expectation that the Company and the Group have adequate resources to continue their operations for the foreseeable future. As a result, the Directors have adopted the going-concern basis in preparing the financial statements.